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Hypoglycemia: Essential Clinical Guidelines

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Abstract

Hypoglycemia is the acute complication of diabetes mellitus and the commonest diabetic emergency and is associated with considerable morbidity and mortality. It can be caused by too much insulin intake or oral hypoglycemic agents, too little food, or excessive physical activity. The level of glucose that produces symptoms of hypoglycemia varies from person to person and varies for the same person under different circumstances. It is characterized by sweating, tremor, tachycardia, palpitation, nervousness, hunger, confusion, slurred speech, emotional changes, double vision, drowsiness, sleeplessness, and often self-diagnosed which may lead to serious symptoms of seizure, cognitive impairment, coma and death. The immediate treatment of hypoglycemia should be known by all the diabetic patients, so that need for hospitalization could be avoided. Hypoglycemia and its severity can be prevented by early recognition of hypoglycemia risk factors, self-monitoring of blood glucose, selection of appropriate treatment regimens, appropriate educational programs for healthcare professionals. The major challenges of the treatment of hypoglycemia are good glycemic control, minimize the risk of hypoglycemia and thereby minimize long-term complications. Hence there is an urgent need to understand the clinical spectrum and burden of hypoglycemia so that adequate control measures can be implemented against this life-threatening complication.

Keywords: blood glucose, diabetes mellitus, glucagon, glycemic index, hypoglycemia, insulin

1. Introduction

The blood sugar level, blood sugar concentration, or blood glucose level is the amount of blood sugar level in the blood. Glucose is required for cellular respiration and is the preferred fuel for all body cells. Plasma glucose concentration is the balance between the rate of glucose entering the circulation and the rate of removal of glucose from the circulation. Circulating glucose comes from intestinal absorption from the ingestion of carbohydrate during the fed state and by the process of glycogenolysis, and gluconeogenesis in the fasting state. Glycogenolysis is the biochemical breakdown of glycogen into glucose which takes place in the cells of the muscle and liver in response to hormonal and neural signals. Gluconeogenesis is the metabolic process of generation of glucose from non-carbohydrate substances such as protein and fat which takes place in the liver and kidney in response to diabetogenic hormones. There are hormones involved in glucose regulation are called glucoregulatory hormones which include insulin, glucagon, amylin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), epinephrine,

cortisol, and growth hormone. Among, insulin and amylin are secreted from the β -cells of islets of Langerhans, glucagon from the α -cells of islets of Langerhans of the pancreas, GLP-1 from the small intestine and colon, and GIP from upper small intestine. If these glucoregulatory or counter-regulatory hormones fail to balance the blood sugar level causes hypoglycemia or hyperglycemia.

Hypoglycemia, also called low blood glucose or low blood sugar, occurs when the level of glucose in blood drops below normal. The term literally means “under-sweet blood”. It may also be referred to as an insulin reaction, or insulin shock. This condition typically arises from abnormalities in the mechanisms involved in glucose homeostasis. Hypoglycemia is the commonest diabetic emergency and is associated with considerable morbidity and mortality. The American Diabetes Association defines the hypoglycemia as any abnormally low plasma glucose concentration that exposes the subject to potential harm [1]. Hypoglycemia is common in insulin dependent diabetic patients and may also occur in patients with non-insulin-dependent diabetes mellitus. It can be caused by too much insulin intake or oral hypoglycemic agents or too little food or excessive physical activity [2]. The other causes or risk factors of hypoglycemia are dosage, combination of anti-diabetic drugs, timing of consuming the drug and anti-diabetic drug with simultaneous use of other interacting drugs. The symptoms of hypoglycemia depend on the level of blood glucose and vary from one person to another person and also vary within the same person under different circumstances [3]. It may range from a very mild with minimal or no symptoms (60–70 mg/dl), to severe hypoglycemia, and neurological impairment (<40 mg/dl) [4].

2. Prevalence of hypoglycemia in diabetes

Hypoglycemia is one of the most feared complications of diabetes treatment [5]. Individuals who take insulin, which includes all people with T1DM and some people with type 2 diabetes, are prone to hypoglycemia [6]. Hypoglycemia commonly occurs in clinical practice as approximately 90% of all patients who receive insulin have experienced hypoglycemic episodes [7]. Furthermore, surveys investigating the prevalence of hypoglycemia have provided some alarming results. The Diabetes Control and Complication Trial (DCCT) reported a threefold increase in severe hypoglycemia and coma in intensively treated T1DM patients versus conventionally treated patients [8]. A meta-analysis study reported that the prevalence of hypoglycemia was 45% for mild/moderate and 6% for severe. Incidence of hypoglycemic episodes per person-year for mild/moderate and for severe was 19 and 0.80, respectively. Hypoglycemia was prevalent among patients on insulin; among, the prevalence of mild-moderate and severe hypoglycemia episodes was 50 and 21%, respectively. Similarly, among patients on the treatment of sulfonylurea, the prevalence of mild-moderate and severe hypoglycemia was 30 and 5%. It was also found 5% of prevalence among those who did not include sulfonylureas in the treatment regime [9].

A population-based study conducted in the UK to determine the frequency and predictors of hypoglycemia in type one diabetic patients. The study findings concluded that type 1 diabetes mellitus patients who are on intensive treatment may experience up to 10 episodes of symptomatic hypoglycemia per week and severe temporarily disabling hypoglycemia at least once a year [10]. It is estimated that 2–4% of deaths occur in people with type 1 diabetes due to hypoglycemia [11]. Hypoglycemia is also equally common in type 2 diabetes, with prevalence rates of 70–80% [12]. Donnelly et al. who conducted a survey with 267 individuals with

type 1 diabetes and insulin-treated type 2 diabetes to record hypoglycemic events over a 4-week period and 155 individuals reported 572 incidents of hypoglycemia. Of these, the rate of hypoglycemia events in type 1 diabetic was 43 per patient per year whereas in type 2 diabetes was 16 events per patient per year. The predictor of hypoglycemia for individuals with type 1 diabetes and insulin-treated type 2 diabetes was a history of previous hypoglycemia and duration of insulin treatment [10]. Similarly other study findings also concluded that hypoglycemia occurs more often than previously reported [12] in insulin-treated type 2 diabetes and with sufficient frequency to cause significant morbidity.

3. Risk factors for hypoglycemia

Several factors influence an individual at risk (**Table 1**) for a hypoglycemic episode. These include a mismatch in the timing, amount, or type of insulin, skipping meals, eating small meal, irregular dietary pattern and lack of physical activity. Additional factors such as alcohol consumption, obesity, elderly people, liver disorders, renal disease, adrenal insufficiency (glucocorticoid or catecholamine deficiencies) and pituitary insufficiency and leukemia which increase the risk for hypoglycemia. Other factors at risk are those who have ingested medication salicylates and those who have surgery with general anesthesia, which places them in an altered state of consciousness and hyper-metabolic state [13].

Another potential risk for hypoglycemia is the use of β -blocker and ACE inhibitor medication in cardiac and hypertensive patients which mask the symptoms of hypoglycemia. β -Blockers inhibit the secretion of insulin and glycogenolysis due to diminishing of adrenergic counter regulation and also conceal the symptoms of catecholamine-mediated neurogenic hypoglycemia such as tremor, palpitation, hunger, irritability and confusion. However sweating remains unmasked and may be the only sign of patients treated with β -blockers [14].

Medical-related factors	Lifestyle-related factors
<ul style="list-style-type: none">• Strict glycemic control• Previous history of severe hypoglycemia• Long duration of type 1 diabetes• Duration of insulin therapy in type 2 diabetes• Lipohypertrophy at injection sites• Impaired awareness of hypoglycemia• Severe hepatic dysfunction• Impaired renal function (including those patients requiring renal replacement therapy)• Sepsis• Inadequate treatment of previous hypoglycemia• Terminal illness• Cognitive dysfunction/dementia	<ul style="list-style-type: none">• Increased exercise (relative to usual)• Irregular lifestyle• Alcohol• Increasing age• Early pregnancy• Breast feeding• No or inadequate blood glucose monitoring <p>Reduced carbohydrate intake/absorption</p> <ul style="list-style-type: none">• Food malabsorption, e.g., gastroenteritis, coeliac disease• Bariatric surgery involving bowel resection <p>Other factors:</p> <ul style="list-style-type: none">• Hypoglycemia unawareness• Number of years since diabetes diagnosis• Time since insulin initiated

Table 1.
Risk factors of hypoglycemia.

4. Causes of hypoglycemia

Hypoglycemia is commonly occur in people with both type 1 and type 2 diabetes taking insulin or certain oral hypoglycemic agents. The common causes of hypoglycemia are:

4.1 Insulin and oral hypoglycemic agents

Diabetes medications such as insulin and Sulfonylureas are the most common causes of hypoglycemia in diabetic subjects [15]. Of these, Insulin is a definite cause of low blood glucose. One reason why newer insulin are preferred over NPH and regular insulin is that they are less likely to cause blood glucose lows, particularly overnight. Insulin pumps may also reduce the risk for low blood glucose. Accidentally injecting the wrong insulin type, too much insulin, or injecting directly into the muscle instead of subcutaneous can cause low blood glucose. The long-acting sulfonylureas such as glibenclamide and chlorpropamide are associated with more severe hypoglycemia than the shorter-acting drugs [16]. Metformin was the most frequent used oral hypoglycemic agents (66.4%) followed by sulfonylurea and the most prevalent combination therapy was metformin/glibenclamide regimen (28.5%). The majority of patients treated with metformin at the time when they were diagnosed with diabetes (45.3%). Hypoglycemic episodes were most commonly reported adverse events with insulin and gastric upset with oral hypoglycemic agents. 60.3% of the patients did not follow regular blood glucose checkup [17]. Several reports reveal that various pharmacological agents like metformin, rosiglitazone, etc., which have wide ranging side effects, including weight gain, hypoglycemia and risk of coronary heart disease [18]. Occasionally episodes of hypoglycemia may occur with metformin, as the most commonly used anti-diabetic drug, due to an imbalance between food intake and dose of metformin [19].

4.2 Food pattern

Eating foods with less carbohydrate than usual without reducing the amount of insulin taken. Timing of insulin based on whether consumption of carbohydrates is from liquids or solids which can affect blood glucose levels. Liquids are absorbed much faster than solids, so timing the insulin dose to the absorption of glucose from foods. The composition of the meal contains the amount of fat, protein, and fiber which can also affect the absorption of carbohydrates.

4.3 Dietary habit

If meal is skip or delay, blood glucose could drop too low. Hypoglycemia also can occur when asleep and have not eaten for several hours.

4.4 Drinking alcohol

Alcohol consumption increase the insulin secretion and makes the liver not to release the glucose effectively into the blood circulation especially if have not eaten enough food within around 6 h and also makes more difficulty to generate new glucose by liver. Hypoglycemia occur overnight if fall asleep after consuming alcohol without eating food among people with diabetes.

4.5 Physical activity

Exercise has plays a vital role and has many potential health benefits. However the exercise can lower blood glucose by utilizing glucose for energy. Nearly half of the individual with diabetes mellitus who exercised an hour during the day may experience a low blood glucose reaction overnight. The factors influencing exercise induce hypoglycemia are the intensity, timing of exercise and dura-tion. Hypoglycemia can occur during, 1–2 h after, or up to 17 h after exercise. Endogenous insulin secretion is reduced up to 40–60% while doing moderate-intensity exercise among non-diabetic individuals. Hence it is mandate that decrease insulin dose or increase glucose intake is recommended before, during or after exercise depending on the intensity of exercise to prevent exercise associated hypoglycemia.

Additionally, recent studies have observed the cruel cycle of counter-regulatory failure between exercise and hypoglycemia. Thus, subsequent two episodes of pro-longed, moderate-intensity exercise can inhibit autonomic nervous system and neu-roendocrine responses by 50%. Similarly, 40–50% of counter-regulatory responses reduced during two episodes of antecedent hypoglycemia due to subsequent exercise [20]. Hence, there is a greater risk of hypoglycemia during exercise among individu-als who have had a previous episode of hypoglycemia. This may be prevented by adjusting pre-exercise insulin dose, and consuming appropriate amounts of glucose.

4.6 Potential causes of in-patient hypoglycemia

Common causes of inpatient hypoglycemia are listed in **Table 2**. One of the most serious and common causes of inpatient hypoglycemia are insulin prescription errors including:

- Misreading poorly written prescriptions
- Confusing the insulin name with the dose

Treatment-related causes	Glucose intake-related causes
<ul style="list-style-type: none">• Inappropriate use of short acting insulin• Incorrect prescription and administration insulin or oral hypoglycemic agent• Mismatch between insulin/oral hypoglycemic therapy and meal or enteral feed• Acute withdrawal of long term steroid therapy• Recovery from stress of critical illness• Polypharmacy• Mobilization after illness• Amputation of limb• Intravenous insulin infusion with or without glucose infusion• Failure to monitor blood glucose adequately especially on Intravenous insulin infusion	<ul style="list-style-type: none">• Reduced carbohydrate intake than normal• Anorexia• Nausea and/or vomiting• Nothing by mouth orders• Delay in serving food tray• Poor coordination in meal and medica-tion timing• Skipping of meal

Table 2.
Etiological factors of hypoglycemia.

- Confusing the insulin strength with the dose
- Transcription errors
- Inappropriately withdrawing insulin using a standard insulin syringe
- Confusion between the prescription of a glucose and insulin infusion for hyperkalemia and glucose and
- insulin infusion to blood glucose control

5. Physiology of glucose counter-regulation

The most metabolically active organ is brain and it is the first organ affected by lower blood glucose level. The brain requires continuous supply of oxygen and glucose to meet the needs of energy requirement as it does not store excess energy and derives almost all of its energy from aerobic oxidation of glucose. Hence brain cells are vulnerable to glucose deprivation and also cannot survive more than 5–6 min without glucose. The sequence of counter-regulatory response will play significant role when the blood glucose levels fall below 70 mg/dl to protect the brain from further deterioration of effects of hypoglycemia.

Decline in Blood glucose levels below the physiological range may trigger hierarchically organized sequence of responses in the non-diabetic individual [21, 22]. It includes release of neuroendocrine hormones or counter-regulatory or anti-insulin hormones, stimulation of the autonomic nervous system (ANS), and manifestation of neurogenic and neuroglycopenic symptoms. Pancreatic beta cells suppressed the insulin secretion when blood glucose levels declines within the physiological range results in reduction of peripheral glucose uptake and increase in hepatic glucose production to prevent true hypoglycemia. In further, declining intra-islet insulin plays an important role for the glucagon response to hypoglycemia by increase the release of glucagon by pancreatic alpha cells [23–25] and pancreatic polypeptide from the pancreas. Similarly catecholamines such as epinephrine secreted from the adrenal medullae and norepinephrine from sympathetic postganglionic nerve terminals and adrenal medulla. Cortisol from the adrenal cortex and growth hormone from the anterior pituitary gland also triggered when blood glucose level falls. The primary physiological fast acting hormones in response to hypoglycemia are glucagon and epinephrine.

Glucagon hormones enhance endogenous glucose production by the process of glycogenolysis and gluconeogenesis and generating glucose substrates such as lactate, pyruvate, alanine, and glycerol. In addition, epinephrine also has similar effects like glucagon in increase of endogenous glucose production and inhibition of utilization of glucose in the peripheral tissue and converts the gluconeogenic pathway. It can also stimulate net renal glucose production. However inhibition of insulin secretion is the primary physiological defense against decrease blood glucose and occurs at a plasma glucose concentration of less than 80 mg/dl. The response of sympathetic nervous system against hypoglycemia is activated by both circulating catecholamines and direct innervation results in increased fat metabolism of lipolysis in adipocytes which release free fatty acid. It is estimated that 25% of the total defense against hypoglycemia by the contribution of free fatty acid. Cortisol and growth hormone are metabolic defense which are released in response to prolonged hypoglycemia; but they have modest significant effect on glucose counter-regulation during acute stage. The actions of these hormones are increasing glucose

production and restraining glucose disposal after 4 h onset of hypoglycemia. It has only 20% of counter-regulatory response compared to the action of epinephrine.

If counter-regulatory mechanism fails to maintain the glucose homeostasis and blood glucose value of 3.0–3.5 mmol/l, may trigger the autonomic nervous system mediated warning symptoms such as sweating, palpitation and hunger to warn subjective awareness of hypoglycemia and provoke feeling of eating to improve blood glucose level. If not consume adequate glucose during this stage, central nervous deprives for glucose, neuroglycopenia develops and cognitive function declines. Counter-regulatory responses to hypoglycemia also referred to as glycemic thresholds and may be altered to higher plasma glucose levels following chronic hyperglycemia [26] or to lower plasma glucose levels following repeated hypoglycemia [27–29]. On the whole, the magnitude of counter-regulatory function is decrease with age 18 and is more obvious in male than in female [30].

6. Hypoglycemia and glycemic threshold

The glycemic threshold has a dynamic and significant role in the activation of counter-regulatory physiological response against the low plasma glucose level [20]. Though the individuals have increased level of glycated hemoglobin (HbA1C) may perceive the symptoms of hypoglycemia at higher blood individuals who undergo intensive glucose level with diabetes [31]. It means sudden and rapid declines of blood glucose from higher level to a lower but not too low and at this level brain started reacting to change and release of counter-regulatory hormones. This phenomenon is called “**relative hypoglycemia**” and it is self-limiting. Brain will usually takes 2–4 weeks to readjust and to improve that relatively reduced circulating glucose levels [27, 31–34].

In contrast, among diabetic patients who are on the intensive treatment of control of plasma glucose level may not perceive hypoglycemia until their plasma glucose is considerably lower than the normal physiological glycemic thresholds [33, 35]. The changes in this glycemic control are highly influenced chronically by persistent hyperglycemia and acutely by antecedent hypoglycemia [12, 35–38]. **Antecedent hypoglycemia** is a condition caused by hypoglycemia itself which impairs and reduces the reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia. An experimental study found that there is a significant reduction in glucagon, epinephrine, cortisol, pancreatic polypeptide responses to next-day of hypoglycemia among antecedent hypoglycemic patients who experienced two episodes with the blood glucose level of 50 mg/dl. It was also demonstrated that antecedent hypoglycemia reduced the neurogenic and neuroglycopenic symptom responses [28]. In later another study investigated the responses of metabolic and neuroendocrine on the effect of morning hypoglycemia to subsequent afternoon hypoglycemia. The findings revealed that only one prolonged, moderate hypoglycemic episode can also blunt the substantial changes of physiological counter-regulatory defense and the neurogenic and neuroglycopenic symptom response to subsequent hypoglycemia [39].

This impaired counter-regulatory responses otherwise called as “**hypoglycemia-associated autonomic failure**” causes reduced neuroendocrine counter-regulatory responses to hypoglycemia and lowered glycemic thresholds for activation of physiological defenses against hypoglycemia, which together lead to a condition called **hypoglycemic unawareness**. During this stage, because of failure to trigger the epinephrine secretion against severe drop in blood sugar, the individuals unaware of hypoglycemic symptoms of sweating, palpitation, anxiety generated by epinephrine. These symptoms are very significantly important to warn the individuals of the

lowering blood glucose level. Same scenario happened in intensively treated type 1 and type 2 diabetic individuals due to shifting of glycemic threshold to lower plasma glucose level [33, 39–42] which further limits the efforts to attain euglycemia [37, 38].

7. Clinical manifestations of hypoglycemia

Hypoglycemic signs and symptoms (Table 3) may occur unexpectedly and suddenly depends on the blood glucose level and may also vary from one person to another. The hyperglycemic individuals who have blood glucose level with 200 mg/dl or greater may feel adrenergic hypoglycemic symptoms when blood glucose suddenly falls to 120 mg/dl or less. Whereas a person with usual blood glucose levels in the low range may not experience symptoms when blood glucose slowly drops under 50 mg/dl and also patients who have had diabetes for many years have decreased hormonal (adrenergic) response to hypoglycemia.

Hypoglycemic symptoms may manifest as neurogenic (autonomic) symptoms and cholinergic-mediated symptoms. Low blood glucose level triggered the neurogenic symptoms by activating the autonomic nervous system which releases the catecholamines (norepinephrine and epinephrine) from the adrenal medullae and acetylcholine from postsynaptic sympathetic nerve endings. Elevated epinephrine levels leads the symptoms and signs of shakiness, palpitations, sweating, nervousness, anxiety, pupil dilation, dry mouth, pallor. The cholinergic-mediated symptoms are hunger, diaphoresis and paresthesia. However, only 20% of the total neurogenic symptom was found during hypoglycemia among epinephrine infusion in intensively and conventionally treated euglycemic type 1 diabetic individuals which indicates that the symptoms of hypoglycemic is multifocal and is mainly araised from efferent pathways of central nervous system [43].

Neuroglycopenic symptoms occur as a result of deprivation of glucose in the brain cells during hypoglycemia. Neuroglycopenic symptoms are very difficult to perceive by an individual rather it is most often recognized by family members, friends and bystanders. These symptoms include irritability, confusion, aphasia, paresthesias, ataxia, headache and the most severe symptoms are seizures stupor, coma, and even death. It can also include transient focal neurological deficits such as diplopia, hemiparesis.

Autonomic symptoms	Neuroglycopenic symptoms
Sweating	Blurred vision
Tingling	Difficulty speaking
Trembling	Feeling faint
Feeling shaky	Difficulty thinking
Feeling hungry	Confusion
Palpitations	Dizziness
Anxiety	Feeling drowsy
	Irritability
Autonomic signs	Neuroglycopenic signs
Tachycardia	Transient Focal Neurological Deficit occasionally
Increased systolic blood pressure	
Pallor	
Diaphoresis	
Mydriasis	

Table 3.
Signs and symptoms of hypoglycemia.

Autonomic	Neuroglycopenic	General malaise
Sweating	Confusion	Headache
Palpitations	Drowsiness	Nausea
Shaking	Odd behavior	
Hunger	Speech difficulty	
	Incoordination	

Table 4.
Edinburgh hypoglycemia scale.

Neurogenic and neuroglycopenic symptoms are manifested by the activation of the sympatho-adrenal system and brain's glucose deprivation. The brain is continuously depends on a circulating glucose for energy and for cognitive function. If blood glucose levels fall causes cognitive dysfunction [44]. The 11 most commonly reported symptoms were used to form the Edinburgh Hypoglycemia Scale [45] and are reproduced in **Table 4**.

8. Levels of hypoglycemia

According to the blood glucose level and manifestation of signs and symptoms in response to low blood glucose level, hypoglycemia can be categorized into Level I, Level II and Level III or mild, moderate and severe hypoglycemia.

8.1 Level I (mild) hypoglycemia

The range of blood glucose level is 54–70 mg/dl. Symptoms include tremor, palpitations, tachycardia, nervousness, sweating and hunger due to sympathetic nervous system is stimulation.

8.2 Level II (moderate) hypoglycemia

The range of blood glucose level is 40–54 mg/dl. It may produce confusion, irritation, inability to concentrate, headache, lightheadedness, memory loss, numbness of the lips and tongue, slurred speech, lack of coordination, emotional changes, drowsiness, and double vision, or any combination of these symptoms due to impaired function of central nervous system.

8.3 Level III (severe hypoglycemia)

In severe hypoglycemia, the blood glucose level is less than 40 mg/dl. Central nervous system function is impaired further. Symptoms may include disoriented behavior, seizures, stupor, or loss of consciousness. During this stage they need help from another as they unable to function because of physical and mental changes.

9. Mechanisms of counter-regulatory responses to hypoglycemia in type 1 diabetes

Type 1 diabetes mellitus is otherwise called insulin dependent diabetes mellitus which occur due to little production of insulin or no insulin from pancreatic beta-cells characterized by hyperglycemia and its associated symptoms. The treatment include for the management of diabetes mellitus is insulin, diet and exercise and

lifestyle modification. Insulin helps to convert the glucose into glycogen and store in the liver and muscles. If there is an imbalance between the insulin administration and food intake leads to hypoglycemia. Physiologically glucagon will be secreted by the pancreatic alpha-cells to convert the stored glycogen into glucose or from non-carbohydrate substances. However in patients with type 1 diabetes for more than years epinephrine is main physiological defense in response to hypoglycemia because glucagon secretory response to hypoglycemia is irreversibly lost. In later, epinephrine response to hypoglycemia also impaired unfortunately among patients with type 1 diabetes undergoing intensive treatment of insulin and at greater risk for recurrent hypoglycemia [46, 47]. There is more than 50% reduction in counter-regulatory responses toward the future hypoglycemia due to repeated attack of hypoglycemia which results in vicious cycle of iatrogenic hypoglycemia-associated autonomic failure and also subsequent hypoglycemia may also leads to antecedent hypoglycemia. Even short durations 20 minutes of antecedent hypoglycemia can produce significant impairment in counter-regulatory responses and also two episodes of hypoglycemia of 70 mg/dl can also blunt subsequent counter-regulatory responses by ~30% in men [48]. Patient may experience severe and significant clinical consequences due to reduced adrenergic sensitivity of poor tissue responsive to circulating epinephrine and deficient responses of glucagon with reduction in ANS counter-regulatory responses. These patients also had reduced β -adrenergic sensitivity compared to patients with normal counter-regulatory responses to hypoglycemia and healthy control subjects [49] and had reduced whole-body tissue sensitivity to epinephrine, which was exacerbated by intensive glycemic control. This reduced tissue responsiveness to epinephrine is an additional contributor to the syndrome of hypoglycemia-associated autonomic failure and reduced tissue sensitivity to epinephrine resulted in decrease endogenous glucose production and less inhibition of insulin-stimulated glucose uptake. Despite with persistent blunted epinephrine response to hypoglycemia, hypoglycemic symptom and β -adrenergic sensitivity responses increase [50] to restore the endocrine and autonomic function. Although controversial, other studies have also stated that with strict avoidance of antecedent hypoglycemia some or all of the features of hypoglycemia-associated autonomic failure can be reversed [51–53].

9.1 Mechanisms of counter-regulatory responses to hypoglycemia in type 2 diabetes

Type 2 diabetes mellitus is a heterogeneous group of disease caused by inadequate secretion of insulin or improper utilization of secreted insulin or both. It may affect all groups of people from children to older adults. Children are more commonly affected nowadays due to rise in childhood obesity. Treatment regime includes diet, exercise, oral hypoglycemic agents, glucagon like peptide-1 analogs, insulin, or combination of these and varies depending on the response to treatment and progressive β -cell failure [54]. The symptoms of hypoglycemia associated autonomic failure among type 2 diabetes depends on age, treatment modality (diet versus oral hypoglycemic agents versus insulin), comorbidity, body fat composition, metabolic control, and the presence of diabetic neuropathies [54, 55]. However, neuroendocrine contributes in glycemic responses to hypoglycemia in advanced type 2 diabetes. The glucagon response to low blood glucose level was also absent in advanced insulin-treated type 2 diabetes. Autonomic and symptomatic responses by glycemic threshold to hypoglycemia were also altered to lower plasma glucose concentrations by recent antecedent hypoglycemia. Hence, the risk for hypoglycemia-associated autonomic failure was high in advanced type 2 diabetes as like those with type 1 diabetes and leads to harmful cycle of recurrent iatrogenic hypoglycemia [46, 55].

10. Inborn errors of metabolism causing hypoglycemia

Non-diabetic hypoglycemia also results from inborn errors of metabolism. Such hypoglycemia most commonly occurs in infancy but can also occur in adulthood. Cases in adults can be classified into those resulting in fasting hypoglycemia, postprandial hypoglycemia, and exercise-induced hypoglycemia.

10.1 Fasting (postabsorptive) hypoglycemia

It is rare; disorders of glycogenolysis can result in fasting hypoglycemia. These disorders include glycogen storage disease (GSD) of types 0, 1, 3, and 4 and Fanconi-Bickel syndrome.

10.2 Patients with GSD

Type 1 and 3 characteristically have high blood lactate levels before and after meals, respectively. Both groups have hypertriglyceridemia, but ketones are high in GSD type 3. Defects in fatty acid oxidation also result in fasting hypoglycemia. These defects can include (1) defects in the carnitine cycle; (2) fatty-acid β -oxidation disorders; (3) electron transfer disturbances; and (4) ketogenesis disorders. Finally, defects in gluconeogenesis (fructose-1, 6-biphosphatase) have been reported to result in recurrent hypoglycemia and lactic acidosis.

10.3 Postprandial (reactive) hypoglycemia

Inborn errors of metabolism resulting in postprandial hypoglycemia are also rare. These errors include (1) glucokinase, SUR1, and Kir6.2 potassium channel mutations; (2) congenital disorders of glycosylation; and (3) inherited fructose intolerance.

10.4 Exercise-induced hypoglycemia

Exercise-induced hypoglycemia, by definition, follows exercise. It results in hyperinsulinemia caused by increased activity of monocarboxylate transporter 1 in β cells.

11. Accidental, surreptitious, or malicious hypoglycemia

Hypoglycemia caused by endogenous hyperinsulinism due to functional β -cell disorders, insulinoma, or the insulin autoimmune syndrome is called as accidental, surreptitious, or malicious hypoglycemia. It may also occur by accidental administration of insulin, or accidental ingestion of an insulin secretagogue such as sulfonylurea because ingestion of an insulin secretagogue causes hypoglycemia with increased C-peptide levels and hypoglycemia caused by exogenous insulin with decrease C-peptide levels reflecting suppression of insulin secretion.

12. Assessment and diagnostic methods

- History collection
- Physical examination

- Diagnostic investigation: It includes
- Glucose—fasting and postprandial blood glucose
- Complete blood count
- Insulin
- C-peptide
- Beta-hydroxybutyrate
- Proinsulin
- Antibodies for insulin and its receptors
- Sulfonylurea and meglitinide screen
- Electrolytes, BUN/Cr, UA
- liver function tests,
- cortisol and thyroid levels, growth hormone level
- Other tests: CT and MRI

Whipple triad is the clinical presentation of pancreatic insulinoma and consists of: fasting hypoglycemia (<50 mg/dl), symptoms of hypoglycemia, immediate relief of symptoms after the administration of IV glucose.

13. Management of hypoglycemia

The aim of the treatment includes correction of glucose deficiency, prevent the complication associated with hypoglycemia and treat the underlying the cause. Treat the patient in the emergency department as shown in the **Figure 1**.

- History collection and physical examination
- Check the blood glucose—capillary blood glucose
- Assess the mental status of the client
- Access intravenous line if needed
- Monitor blood glucose level
- Administer 15 g of fast acting glucose in the form of glucose tablets or glucose containing fluids, candy or food. For, e.g., three or four commercially prepared glucose tablets; 4–6 oz. of fruit juice or regular soda, 6–10 hard candies, 2–3 tsp. of sugar or honey is appropriate if the patient is able to take orally
- Check for blood glucose 15 min later.

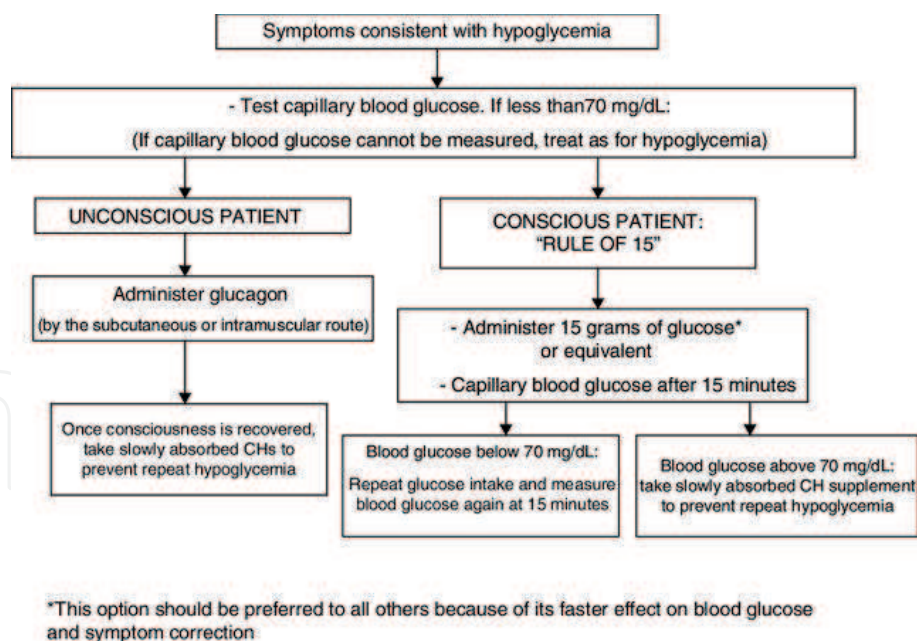


Figure 1.
 Schematic representation of emergency management of hypoglycemia.

- Instruct the patient to eat protein and carbohydrate containing snack to maintain their blood glucose after 60 min if the blood glucose is higher than 70 mg/dl
- Treatment is repeated with 15 g of carbohydrates if glucose level is remains less than 70 mg/dl after the initial intake of 15 g of glucose. It may be probably repeated up to 1–3 times
- Instruct the patient to avoid adding more table sugar to juice, even “unsweetened” juice, which may cause a sudden increase in glucose, resulting in hyperglycemia in later hours.
- Administer parenteral therapy with 25% dextrose if unable to take oral foods
- Administer inj. glucagon 1.0 mg subcutaneous/intramuscular can be used especially in type 1 diabetes mellitus.
- The somatostatin analog octreotide can be used to suppress insulin secretion in sulfonylurea-induced hypoglycemia.
- Identify and treat the underlying cause

13.1 Management of hypoglycemia in the unconscious patient

- Assessment of glasgow coma scale
- Monitor airway, breathing, circulation
- Constant monitoring of blood glucose level
- Administer 1 g of glucagon subcutaneously or intravenously
- Administer 50% dextrose in 25–50 mL of water intravenously

- Check the patient for regaining from the state of unconsciousness. If hypoglycemic state extends for more than 5 h results in profound hypoglycemia which may cause permanent brain damage.
- Administer IV Mannitol and dexamethasone, IV glucose with constant glucose monitoring to necessary until regain from the state of unconsciousness to conscious and restore normal brain function

13.2 Management of non-diabetic hypoglycemia

Depend on the underlying etiology

- Discontinue the offending drugs or reduce their doses
- Treat the underlying critical illnesses
- Replace the cortisol and growth hormone if levels are deficient.
- Surgical, radiotherapeutic, or chemotherapeutic reduction of a non-islet cell tumor.
- Surgical resection of an insulinoma is curative
- Medical therapy with diazoxide or octreotide can be used if resection is not possible and in patient with a non-tumor beta cell tumor

13.3 Health education

- Consult with a dietitian to develop or adjust meal plan to maintain consistency in carbohydrates at meals by calculating grams of carbohydrates so that plan for medication and/or insulin.
- Self-monitoring of blood glucose to detect the episodes of hypoglycemia at the earliest. Self-monitoring of blood glucose level should give an idea of what makes the blood glucose level drop.
- Do not skip meal and balance the meal plan with insulin or oral hypoglycemic agent.
- Quit alcohol and smoking.
- Maintain the body weight.
- Follow medication dose regularly.
- Avoidance of exercise while having the symptoms of hypoglycemia.
- Ingestion of carbohydrate especially rapidly absorbed glucose during the symptoms of hypoglycemia.
- Remember and follow rule of 15 which means 15 g of glucose raise 50 mg/dl in 15 min during hypoglycemia state.

- Intravenous glucose is the preferable treatment of severe hypoglycemia, particularly that caused by a sulfonylurea.
- Keeping the hypo box hypoglycemic kit which contains glucose, glucagon, juice, etc.
- Instructing the family members and care givers about usage this kit, check for expiry date and replacing the used content in the kit.
- Always carry the sweetener which contains easily absorbable simple sugar and identity card.
- Regular check-up and follow-up care.

14. Conclusion

Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment. This chapter emphasis on causes and risk factors of hypoglycemia, recognition of symptoms of hypoglycemia, glucose regulatory and counter regulatory mechanism, management and prevention of hypoglycemia thereby prevent the potential complications of hypoglycemia. Health care professionals have a major role in educating clients with diabetes mellitus about hypoglycemia and to follow their hypoglycemia management plan while caring the clients.

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Conflict of interest

The author declares no conflict of interest.

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